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EDITORIAL

Fludrocortisone with hydrocortisone in sepsis: new evidence in an ongoing debate

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The use of systemic corticosteroids in sepsis is a key topic. Current guidelines suggest the use of low dose of intravenous hydrocortisone for adults with vasopressor-dependent sepsis [1, 2]. A burning question is the need for additional enteral use of fludrocortisone, which is not recommended by the current guidelines [1, 2]. Fludrocortisone acetate itself is an inactive pro-drug that is activated by hydroxylation by hepatic esterases or pseudo-esterases. It has strong mineralocorticoid activity but minimal glucocorticoid activity. Whether mineralocorticoid or non-mineralocorticoid effects, such as immune or vascular [3], provides additional clinical benefits on top of hydrocortisone, is uncertain (Table 1).

Landmark randomized controlled trials (RCTs) comparing either hydrocortisone or hydrocortisone plus fludrocortisone with placebo found a general improvement in clinical outcomes. In the CORTICUS trial, 499 patients with septic shock showed no overall difference in mortality, but quicker shock reversal, when comparing hydrocortisone with placebo [4]. The ADRENAL trial randomized 3800 patients with septic shock undergoing mechanical ventilation, and reported no difference in 90-day mortality between hydrocortisone and placebo but faster resolution of shock [5]. The first RCT published in 2002 comparing hydrocortisone plus fludrocortisone with matching placebos randomized 299 patients with septic shock and found a reduction in 28-day mortality in the group using hydrocortisone plus fludrocortisone [6]. In the APROCCHSS trial enrolling 1241 patients with septic shock, there was a reduction in 90-day mortality in those who received hydrocortisone plus fludrocortisone 50 µg orally compared with placebo, and this was associated with more vasopressor- and organ failure-free days [7]. Only two RCTs compared directly hydrocortisone plus fludrocortisone with hydrocortisone. The first was a 2×2 factorial open-labelled trial (COIITS trial), involving 509 patients with septic shock and multiple organ dysfunction [8]. This trial reported a 3% (95% confidence interval [CI], −12% to 6%) absolute reduction in in-hospital mortality in favour of hydrocortisone plus fludrocortisone, albeit non-statistically significant. There were no statistically significant differences for other main clinical outcomes. The second was a small, 3-arm, single centre, open-label trial of 66 adults with septic shock which found a non-significant 4.6% (95% CI −33 to 23) absolute reduction in short-term mortality in favour of hydrocortisone plus fludrocortisone compared with hydrocortisone alone [9].

Because of the sparsity of trials directly comparing hydrocortisone plus fludrocortisone with hydrocortisone alone, some researchers have used the entire evidence base to indirectly estimate the effect of hydrocortisone plus fludrocortisone against hydrocortisone using network meta-analysis. In one such exercise, 17 trials ($n=7688$ patients) were analysed within a Bayesian framework [10]. The pooled summary combining direct and indirect evidence was in favour of hydrocortisone plus fludrocortisone compared with hydrocortisone alone (risk ratio [RR] 0.88, 95% CI 0.74 to 1.03, 94.3% probability of superiority) for last follow-up all-cause mortality. However, uncertainty remained and the majority of evidence was indirect. Similar results were achieved by another network meta-analysis, which also included observational studies such as target-emulated trials [11]. Both reviews concluded that large, multicentre RCTs are needed with a head-to-head comparison of hydrocortisone plus fludrocortisone against hydrocortisone alone. An individual-patient meta-analysis observed no benefit of hydrocortisone

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Table 1 Pros and cons for the use of fludrocortisone together with hydrocortisone in patients with septic shock

Domain	Pro	Con
Theory	Mineralocorticoid and non-mineralocorticoid effects on vasculature, kidney, and immune system	Uncertain mechanism(s) of purported benefit
Physiology	Regulation of salt and water balance though actions on unidirectional Na^+ transport across the epithelium	No clear pharmacodynamics effect seen when dosed orally in patients in septic shock
Pharmacodynamics / Pharmacokinetics	When administered orally, there was a serum increase across virtually all patients	Inconsistent pharmacokinetics when dosed orally in patients in septic shock
Experimental models	Administration of aldosterone could restore vascular tone by increasing alpha-1 receptors expression. Models show that for some tissues, both mineralocorticoid and glucocorticoid effects are need to counteract sepsis effects, such as cardiomyocites	Not all effects observed with aldosterone was reproduced by fludrocortisone. Lack of evidence in humans and the challenge to translate murine and other animal models to humans
Clinical evidence	Clinical trials that showed a reduction in mortality when comparing hydrocortisone plus fludrocortisone versus placebo	Few and inconclusive studies comparing directly hydrocortisone plus fludrocortisone with hydrocortisone alone. Evidence mainly from indirect comparisons in network meta-analysis

alone in mortality of patients with septic shock, but an interaction towards survival benefit in those who used fludrocortisone [12]. A large emulated target-trial, using real-life data, observed a similar magnitude of reduction in mortality (−3.7%, 95% CI −4.2 to −3.1) to the COIITS trial in adults with norepinephrine-treated septic shock [13]. Exploratory re-analyses indicated that the mortality benefits of adding fludrocortisone to hydrocortisone would be mainly seen when the source of shock was community-acquired pneumonia [14, 15].

In the context of these uncertainties, Walsham et al. report the Fludrocortisone Dose Response Relationships and Vascular Responsiveness in Septic Shock (FluDReSS) phase-2 trial [16], aiming to answer important research questions regarding fludrocortisone pharmacokinetics and pharmacodynamics in a septic shock population. FluDReSS was a multicentre, randomised, open-label study in 153 patients with septic shock receiving intravenous hydrocortisone (200 mg/day) assessing three doses of fludrocortisone (50, 100 or 200 µg daily orally for 7 days), and comparing these with a group not receiving fludrocortisone. There were no significant differences between groups in the primary outcome, time to shock resolution, nor recurrence of shock, indices of organ failure or other secondary outcomes. The sample size was not powered to address a mortality impact but there was a possible reduction to lower 28-day mortality rates at higher doses of fludrocortisone.

All patients received the assigned drug and missed doses were rare. Limitations included the lack of blinding, no standardization of haemodynamic targets and vasopressor weaning, and early trial cessation due to slow recruitment, with only 50% of the planned sample size achieved. Because of the limited sample size, the interpretation of clinical outcomes is challenging. Importantly, there was no signal to indicate harm.

The FluDReSS results on pharmacokinetics and pharmacodynamics are interesting albeit limited. These provide new insights but also important questions to better understand the use of adjunctive fludrocortisone therapy in sepsis. Fludrocortisone was measured post-dose in 74 (74/115, 64%) patients from the three fludrocortisone groups and was detected in plasma in 97% at 3 h post-dose. The median concentration was 261 ng/L [interquartile range: 156–334], but with considerable individual variability between patients. Adjusting for pre-dose levels and drug elimination, there was no difference between the three different dosages. The correlation between the vasoactive-inotropic score (VIS) and plasma fludrocortisone levels was weak at baseline, and virtually no correlation was observed at 3 h post-dose. A previous pharmacokinetic study found that oral fludrocortisone resulted in detectable drug in the plasma in only two-thirds of septic shock patients, and also found large inter-individual variability in plasma concentrations [17].

This study highlights the marked variability in plasma levels of fludrocortisone, likely related to inconsistent intestinal absorption ± variable hepatic metabolism. While standard liver function tests were similar between groups, these do not necessarily indicate functionality in terms of xenobiotic metabolism. From a pharmacodynamic perspective, no differences were seen in blood pressure, plasma electrolytes nor fluid balance, suggesting a minimal mineralocorticoid effect, again possibly related to variable absorption and/or metabolism issues.

Even after testing three dose regimens, as done in FluDReSS, it is not clear which should be used in future RCTs, or whether an intravenous formulation, providing more reliable pharmacokinetics, can be made and tested.

Whether the pooled (indirect) evidence in favour of the combination is viewed as sufficient evidence is open to debate. Nonetheless, the combination is not currently recommended by guidelines and its use in adults with vasopressor-dependent sepsis is not widespread. An adequately powered RCT to definitively answer this question would be helpful. However, such a study, assuming the best estimate we have on absolute mortality reduction, would need over 5000 patients and is unlikely to be performed [13].

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